UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/384,959	08/27/1999	RAM SASISEKHARAN	M0656/7046HC	8533

23628 7590 11/17/2003

WOLF GREENFIELD & SACKS, PC
FEDERAL RESERVE PLAZA
600 ATLANTIC AVENUE
BOSTON, MA 02210-2211

EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/384,959	SASISEKHARAN ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-34 and 46-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-34 and 46-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants cancellation of claims 1-29, 35-45 and 50-57 and amendment of claims 30 and 46, is acknowledged. Applicants' arguments filed on 8/27/2003, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 30-34, and 46-49 are at issue and are present for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30-34 and 46-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As stated in the previous office action, claims 30 (31-34 dependent on) and 46 (47-49 dependent on) are indefinite in the recitation of "having a modified product profile, wherein the modified product profile of the modified heparinase II is at least 10% different than a native product profile of a native heparinase II," as the specification fails to teach which what the product profile of a native heparinase II is and how one determines or what a product profile is that is 10% different from such a native product profile. While page 20, lines 21-32, discuss applicants intent as to a "modified product profile", it remains unclear how one would determine a product profile that is 10%

different and thus the metes and bounds of the genus of those methods of using a modified heparinases are unclear.

In response to this rejection, applicants traverse that it is clear from the common language of the terms as well as the teachings of the specification that a native product profile of a native heparinase II is simply the set of enzymatic products of a reaction with native heparinase II on a substrate of the enzyme and that "native" merely is used for what is the accepted common usage of the word.

Applicants explanation and discussion of the terms "native" and "modified" are understood, however the reason for the current rejection is because it is unclear how one determines or what a product profile is that is **10% different** from such a native product profile. With respect to this issue for which the rejection was and is currently based, applicants argue that "the difference in product profiles can be assessed according to the difference in the number of types of enzymatic products, the difference in the amount of a particular type of enzymatic product or simply the difference in the amount of enzymatic products *in toto* produced by the enzymes" and that it would be readily apparent to one of skill in the art that the results of the enzymatic reactions can be given in quantitative form and the presence of a 10% difference between the values of the native and modified heparinase II product profiles can be easily assessed. Applicants argument is not found persuasive, because while one of skill in the art would know of a number of ways that the modified product profile could be 10% different from the native product profile, it is unclear without further direction and/or explanation what is encompassed by a product profile that is 10% different from a different product

profile, as there are so many different ways that one product profile may be different form another, as pointed out by applicants. Thus it is unclear what is encompassed by above recitations.

The previous rejection of the recitation of " a native product profile of a native heparinase II" is withdrawn in light of applicants comments that "a native product profile of a native heparinase II" is simply "the product profile of a native heparinase II" It appears that the previous confusion is the result of the use of the term "native" twice within the referred to recitation, as it is believed that the "product profile" of a native heparinase is always a "native product profile", with or without the further specification that the product profile is a "native product profile".

The previous rejection of claims 30 (31, 33, and 34 dependent on) and 46 (47-49 dependent on) as being indefinite in that it is unclear what applicants consider to be encompassed by a "modified heparinase" is hereby withdrawn based on applicants amendment of the claims and applicants that those heparinases encompassed by modified heparinase II molecules must comprise the amino acid sequence of the mature peptide of SEQ ID NO: 2 or conservative substitutions thereof as defined on page 17, line 22 – page 18 line 3.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30, 33, 34, 46, 47 and 48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for those methods of cleaving a heparin-like or heparan sulfate-like glycosaminoglycan comprising contacting said heparin-like or heparan sulfate-like glycosaminoglycan with a modified heparinase II comprising SEQ ID NO: 2 with a specific substitution at histidine 440 or cysteine 348, does not reasonably provide enablement for those methods of cleaving a heparin-like or heparan sulfate-like glycosaminoglycan comprising contacting said heparin-like or heparan sulfate-like glycosaminoglycan with any modified heparinase II having the amino acid sequence of the mature peptide of SEQ ID NO: 2 and conservative substitutions thereof, wherein said modified heparinase II contains at least one amino acid residue that has been substituted with a different amino acid residue selected from those residues which correspond to a cysteine at position 348, a histidine at position 238, 252, 347, 440, 451 and 579 and any residue at positions 446-451 of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In response to this previous rejection applicants have amended claims 30 and 46 such that they are drawn to the claimed methods of use of the recited "modified heparinase II" molecules having the recited functional characteristics (See also above and previous 112 2nd paragraph rejection).

Applicants traverse this rejection on the basis that one of ordinary skill in the art is sufficiently enabled to make the modified heparinase II molecules of the claims to test the modified heparinase II molecules for the desired functional activity (see also above 112 2nd paragraph rejection) and to use the modified heparinase II molecules in the desired methods.

Applicants continue to traverse this rejection on the basis that the claims provide a set of residues that can be modified to produce molecules with altered activity and the recitation of these residues in combination with teachings of the disclosure and extensive working examples provides adequate guidance to one of skill in the art to produce and use a modified molecule with the desired activity.

This is not persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants as claimed by applicants (i.e., with the claimed functional limitations (See above 112 2nd paragraph rejection) and the claimed structural limitations) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

The claimed genus remains inadequately enabled with respect to the particular structure to function/activity relationship disclosed for the taught species and the genus claimed. It is the combination of applicants claimed genus of all modified heparinases with the corresponding substitutions (i.e. nonconservative substitutions), as well as the functional limitation that the claimed mutants have a modified product profile that is at least 10% different than a native product profile of a native heparinase II (See also above 112 2nd paragraph rejection) or the claimed mutants have a k_{cat} value that is at least 10% different than a native heparinase II k_{cat} value, that results in the claimed genus not being enabled.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
11/10/2003